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SEPTEMBER 16, 1985

CHEMICAL ENGINEERING

NEWS

BULK DRUGS

Production moves away from U.S.

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SEPTEMBER 16, 1985

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Cover: Chemical operator at Merck's Elkton, Va., plant telephones data from drying of a batch of thienamycin before transferring the antibiotic to the next stage of production. Photo by Bob Day

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Business

Plastics intermediates production has fallen this year; as the general economy has slowed so have the markets for vinyl chloride, styrene, and toluene diisocyanate. **Page 15**

Government

Members of House committee criticize proposed reauthorization bill for Superfund; some claim it isn't strong enough, others score provisions such as that which pre-empts state standards. **Page 23**

Science

When Fermilab's 1-TeV colliding beam accelerator begins proton-antiproton collision experiments in 1986, it will be the highest energy accelerator in the world for particle research. **Page 62**

Isolation and characterization of a tunichrome, a bright yellow pigment found in blood of tunicates, may give a clue as to how the marine organism concentrates metals in its blood cells. **Page 67**

Product Report

Although the U.S. will consume a third of the medicinal drugs made this year worldwide, only a fourth will be manufactured in this country. **Page 25**

Production Slows For Plastics Intermediates

As growth in economy slackens and exports ease, demand declines for vinyl chloride, styrene, and toluene diisocyanate

Bruce F. Greek, C&EN Houston

Producers of vinyl chloride, styrene, and toluene diisocyanate (TDI) are having the year they reluctantly expected. Production of their end-use products, mainly various fabricated plastics and elastomeric items, will be down. Profits from making and selling the intermediates also likely will fall, even as prices for the two aromatic intermediates increase because of the rise in benzene prices.

The lowered production and profitability result from a maturing of the recovery after the recession. The general economy has slowed substantially in its growth, and this is reflected in housing and transportation, segments of the consumer products industry that require large shares of the production of these plastics intermediates.

Next year, minor improvement in demand for these intermediates has been forecast as a result of expected slight economic improvement. If this forecast proves to be accurate, production of the three major volume intermediates could return to the level of 1984, with the possible exception of TDI. Although production of TDI will recover somewhat, it will be hurt by increasing shifts toward another isocyanate—*p,p'*-methylene diphenyldiisocyanate (MDI)—which also is used in making polyurethanes. Export losses, however, could limit the production gains of these intermediates.

Longer term, the outlook for these plastics intermediates will mirror the recent past, reflecting quite closely economic conditions as they affect sales of autos, houses, furniture, packaging, and consumer disposables. Domestic consumption of these intermediates likely will trend higher as a function of the general growth in the gross national product.

However, production will not necessarily follow domestic consumption. Exports of these intermediates have accounted for a significant part of their production, whereas imports have been small. Exports now are declining as a result of new plants coming on stream in various parts of the world. Imports, at least for styrene, are growing rapidly. The net change in exports over imports for all of these plastics intermediates could reduce production in spite of gains in domestic consumption.

Key Chemicals

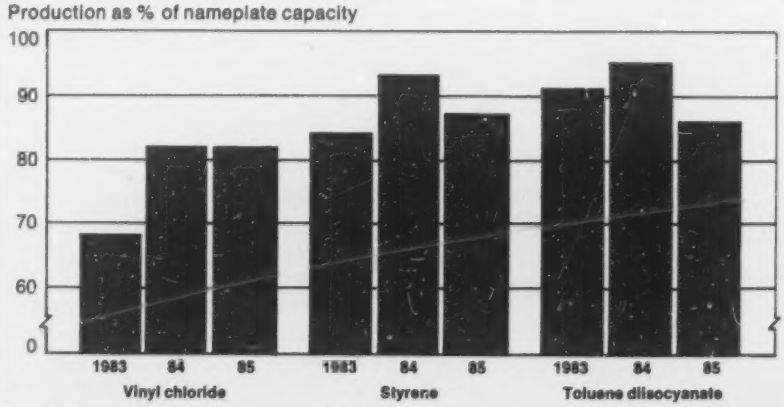
These changes in production, which are expected as a result of changes in foreign trade, cloud forecasts. For example, exports of these plastics intermediates, especially styrene, were expected to decline more this year than they have so far. Styrene exports held up early in 1985 because of startup difficulties at some of the new foreign plants. As these difficulties are overcome and as production nears a level needed to meet demands for their local consumption, foreign buying from U.S. sources will decline more.

Plant use could decline unless some of the presently operating capacity is shut down. Because some plants have been shut down for long periods and a few plants have been scrapped, a drop in capacity seems likely to occur if export markets keep declining. Consequently, the list of players in this scenario for styrene, TDI, and vinyl chloride will change by the end of this decade.

For details of the near-term outlook for styrene, TDI, and vinyl chloride, please see the following pages.

Plant utilization falls in 1985

Production as % of nameplate capacity



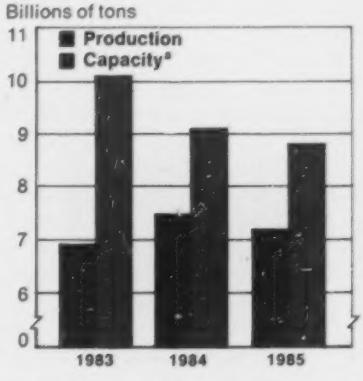
Sources: International Trade Commission, C&EN estimates

Vinyl Chloride

$CH_2=CHCl$

- ***Demand down***
- ***Capacity lower***
- ***Prices weak***

PRODUCTION/CAPACITY



a First quarter; includes some shut-down capacity.

MAJOR PRODUCERS

Dow Chemical, Formosa Plastics, Georgia-Gulf, B. F. Goodrich, PPG Industries

HOW MADE

Dehydrochlorination of ethylene dichloride made by reacting chlorine with ethylene

MAJOR DERIVATIVES (U.S.)

Vinyl polymers nearly 100%

MAJOR END USES (U.S.)

Fabricated plastic items nearly 100%

FOREIGN TRADE

Exports—declining to I billion lb in 1985, imports—rising to more than 150 million lb in 1985

PRICES

21 cents per lb

Vinyl chloride producers are facing declines in demand and price, and their success in dealing with these problems may well determine the future health of the vinyl chloride business.

Forecasts of production of vinyl chloride in 1985 group at around 7.2 billion lb. Production in 1984 was slightly more than 7.5 billion lb. Some optimistic estimates of 1985 production are as much as 7.4 billion lb, but that is still below 1984 output. Pessimistic estimates now call for production to be down 10% in 1985 to about 6.7 billion lb.

The pessimistic forecast stems from the fact that, though first-quarter production of the monomer was high (as it historically is) because of strong demand for polyvinyl chloride pipe used in construction, pipe demand now is down and pipe producers and consumers are reducing their inventories, much as they did in third-quarter 1984. Vinyl chloride producers also know that pipe demand slumps in the third quarter, and they are reducing production accordingly.

Some industry observers believe second-quarter production of vinyl chloride fell to an annualized rate of 6.4 billion to 6.6 billion lb, and that third-quarter output will slow to 6 billion lb a year. A pickup in the fourth quarter, following historical trends, could bounce the production level back to about a 7 billion lb-a-year rate. Such a pickup might be even larger if a predicted strong increase in housing construction occurs in 1986.

Producers of vinyl chloride still face substantial overcapacity, even though some capacity was scrapped in the early 1980s. Currently some of the 8.8 billion lb of nameplate capacity is shut down. The practical operating capacity now may be about 8 billion lb per year, possibly less for all of 1985 because some producers have been making leisurely turnarounds of their plants.

If the total operating capacity for 1985 averages 8 billion lb, and total production reaches 7.2 billion lb, then the average operating rate for vinyl chloride will be a respectable 90%. However, if actual production amounts to close to the 6.7 billion lb level, the rate becomes a less-than-satisfactory 84%.

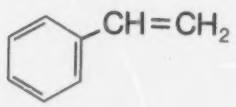
Currently, operating rates are lower than the estimated annual rate, and overcapacity is causing dire problems for vinyl chloride pricing. The list price for vinyl chloride is 28 cents a lb, less a 25% temporary voluntary allowance of 7 cents. But actual selling prices are about 18 cents a lb, possibly less. Some cost relief is afforded by the current low price for feedstock ethylene, about 14 cents a lb. Unfortunately, less than half of the vinyl chloride molecule is ethylene. Chlorine, 57% of the molecule, has firmed in price recently, but electrolysis plant operating rates are down from the past winter. Vinyl chloride consumes about 40% of chlorine production.

Almost all vinyl chloride is polymerized. U.S. sales and captive use of polyvinyl chloride (PVC) and of copolymers declined 3.7% in the first half of 1985 compared with first-half 1984, according to the Society of the Plastics Industry's Committee on Resin Statistics. The decline is less for pipe uses, which account for 45% of PVC consumption, at 2.1%. None of the other end uses of PVC take much more than 10% and most are smaller.

Several unsuccessful attempts have been made this year to raise PVC selling prices. Any increases in PVC prices should quickly come back to the monomer producers and help their low or absent profitability.

Exports of vinyl chloride give producers another problem. Because of the usual export deterrents—the strong dollar and new foreign capacity—exports of vinyl chloride could decline as much as 200 million lb in 1985 to less than 900 million lb. Imports may rise as much as 50 million lb, for a loss in net exports of nearly 25%.

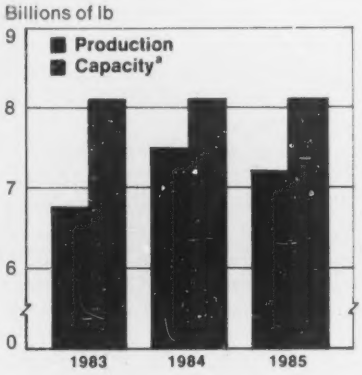
CIRCLE 26 ON READER SERVICE CARD →



Styrene

- ***Demand down***
- ***Capacity expanded***
- ***Prices higher***

PRODUCTION/CAPACITY



[a] First quarter; includes some capacity not operating.

MAJOR PRODUCERS

American Hoechst, Arco Chemicals, Cosmar, Dow Chemical, Monsanto

HOW MADE

Dehydrogenation of ethylbenzene; coproduction with propylene oxide

MAJOR DERIVATIVES (U.S.)

Polystyrene 60%, styrene-butadiene rubbers and latices 15%

MAJOR END USES (U.S.)

Fabricated plastics and rubber products almost 100%

FOREIGN TRADE

Exports—falling below 1 billion lb in 1985, imports—rising to more than 150 million lb in 1985

PRICES

26 to 30 cents per lb

Many of the changes occurring in the U.S. styrene industry have been forecast during the past two years. However, others have not. Small producers, expected to leave the business because of chronic overcapacity, have continued to operate. Conversely, one large producer, American Hoechst, will sell its plants. Exports, expected to decline radically, are declining slowly and behind schedule.

The sale of American Hoechst's styrene operations to Huntsman Chemical will not necessarily reduce industry capacity to make styrene. Because the sale is scheduled to be completed at the end of this month, plans for any changes in operation of the acquired plants haven't yet been announced by Huntsman. Included in the agreement are a 1 billion lb-a-year styrene plant at Bayport, Tex., and two polystyrene plants, at Chesapeake, Va., and Peru, Ind., with a combined capacity of 500 million lb a year.

Styrene capacity has risen during 1985. In May, formal dedication ceremonies were held by Cosmar, a joint venture of Cosden Oil & Chemical (a subsidiary of American Petrofina) and Borg-Warner Chemicals, to mark the conclusion of an expansion of its plant at Carville, La., by 200 million lb to 1.5 billion lb annually. This addition brings U.S. capacity to about 8.3 billion lb a year. Another 750 million lb of currently idle capacity could become available, although most of it has been shut down for more than two years, making future operation unlikely. Further debottlenecking could add a small amount of capacity to the 8.3 billion lb. Debottlenecking, however, likely will be below normal this year because of the low profitability that producers have faced for some time.

The average operating rate in 1985 is difficult to estimate because demand could change later this year. As 1985 began, production was running about 9% below the 1984 rate, according to International Trade Commission (ITC) estimates. Industry sources report that output improved during the second quarter, but may have slowed again in this quarter. For the whole year, estimates of styrene production cluster around 7.2 billion lb, down less than 4% from production in 1984, which was estimated at 7.5 billion lb.

Estimates of the decline in styrene output for 1985 range between none and 8%, putting production between 7.5 billion and 6.9 billion lb. If the Cosmar expansion in capacity is available for nine months of 1985, and other minor additions are available, then operable nameplate capacity likely will total 8.3 billion lb for the whole year. Therefore, the average operating rate will range from 83 to 90% of nameplate capacity.

The biggest factor in the range of estimates for styrene production during 1985 will be the net of exports less imports. Exports of styrene in 1984 were nearly 1.2 billion lb, or 16% of production. Imports were much more modest at just over 100 million lb. Exports in 1985 may decline 25% to under 900 million lb, and imports may rise by half to more than 150 million lb. The net of exports then would fall to 750 million lb, down about a third. However, if new capacity coming on stream in other countries operates more reliably than it has so far, and the strength of the dollar holds up, U.S. exports of styrene could fall more than anticipated and imports also might rise more than anticipated. The result could be that production will be 7.0 billion lb or lower in 1985.

Styrene producers can get little help from the major uses of polymer material. Polystyrene production increased during early 1985, but the month-to-month gains now are smaller. Other uses also have met with production declines. With small growth forecast for the economy during the second half of 1985, gains in demand for consumer products containing styrene will not offset a greater than expected decline in the net of exports less imports.

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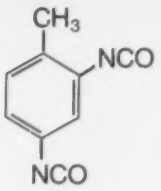
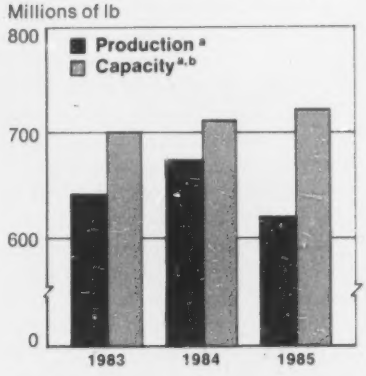
Key Chemicals

Toluene Diisocyanate



- ***Demand weakening***
- ***Capacity up slightly***
- ***Price discounted***

PRODUCTION/CAPACITY



a Mainly 80/20% mixtures of 2, 4- and 2, 6- isomers.
b First quarter; includes some capacity not operating in 1985.

MAJOR PRODUCERS

BASF Wyandotte, Dow Chemical, Mobay Chemical, Olin, Rubicon Chemicals

HOW MADE

Nitration of toluene, followed by reduction to diamine, reaction with phosgene, purification, and recovery of coproduct hydrochloric acid

MAJOR DERIVATIVES (U.S.)

Polyurethanes almost 100%

MAJOR END USES (U.S.)

Flexible polyurethane foams 85%, polyurethane coatings 5%

FOREIGN TRADE

Exports—declining slightly to about 135 million lb in 1985, imports—negligible

PRICES

93 cents a lb

Like that for other major-volume polymer materials, demand for toluene diisocyanate (TDI) is declining as demand for products containing the polymers made from this plastics intermediate wanes. Whether a recovery will occur late in 1985 is debatable.

The decline in production of TDI in 1985 from last year's almost 675 million lb could be greater than current forecasts of about 8%, for a 1985 production total of about 620 million lb. After a good first quarter with output at an annual rate of more than 640 million lb, second-quarter production fell to well under a 600 million lb-per-year rate. During the third quarter, production has not risen appreciably, according to some industry sources, but the third quarter historically is the low one for TDI production.

A pickup in TDI production often occurs in the fourth quarter, raising hopes for total 1985 production of close to 620 million lb or possibly higher. To have a significantly higher total production for 1985, a shutdown plant may have to be restarted early enough to provide additional output during the fourth quarter. If the fourth-quarter pickup fails to develop, then the total for 1985 could be down almost 10% from 1984 to about 610 million lb. If TDI production falls to this level, it would be less than that for 1983 when production was recovering well from the recession.

Total TDI nameplate capacity is 720 million lb, but this includes an 80 million lb-a-year plant that Olin shut down almost a year ago for an indefinite period. Therefore, TDI operating capacity now is 640 million lb a year. To reach an annual production of 620 million lb in 1985 without the Olin plant, all of the remaining capacity would have to be run at an average of 97% of nameplate capacity. Debottlenecking could increase capacity another 5% or so this year, or some 30 million lb. Such added capacity, however, can't be counted on throughout the year. If production does amount to 610 million lb, operating plants will average a rate of 95% of nameplate capacity at the beginning of 1985. These high operating rates could strain plants and further spur debottlenecking efforts.

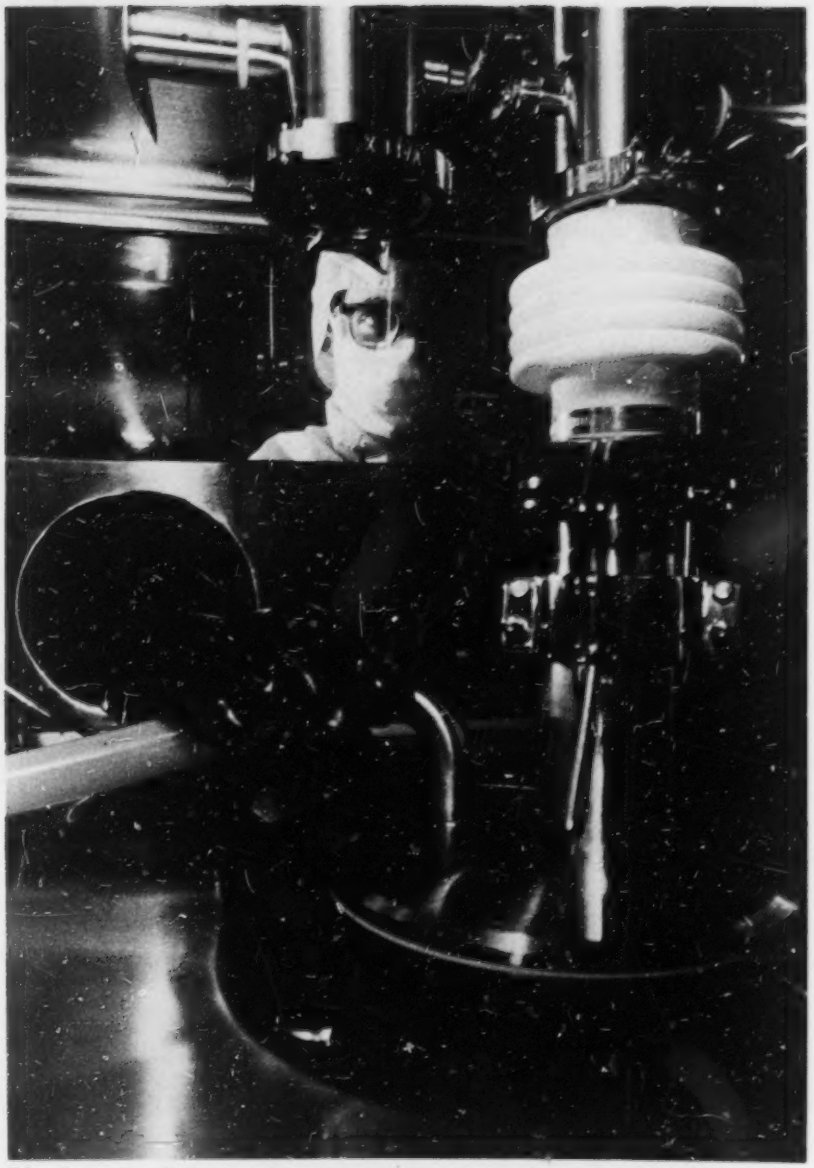
The drop in TDI production this year will result from several factors. One is a slowly continuing decline in exports of TDI. Exports in 1985 may total 135 million lb, but they could be as low as 120 million lb, down about 10% from 1984 exports.

Another is a falloff in demand for the major end uses of flexible polyurethane foams, such as furniture (including bedding and carpet underlay) and automobiles, buses, and trucks. The furniture uses of polyurethane foams are strongly influenced by housing construction. During the late spring and early summer, housing construction trended downward, reducing the potential for furniture sales later this year. Other than building of inventory by furniture manufacturers and retailers, demand for polyurethanes, and in turn TDI, will be lackluster.

The bedding area for polyurethane foam also faces severe competition and may not return to the demand levels of the early 1980s for several more years. A major part of the demand problem in bedding is the success in sales of waterbeds. One industry source estimates that waterbeds now account for 15% of mattress sales, cutting into the market for foams, which has been growing very slowly. Waterbed demand will continue to grow, reducing urethane foam consumption for bedding.

Automotive uses of flexible polyurethane foams are extensive, but these are dominated by seating. Most seating now is molded of a fire-retardant foam. Because of the downsizing of cars, consumption of foam per car is more than 10% lower than it was five years ago. Prospects for growth in automotive uses are better than in other major end uses, but they still are quite small relative to past growth.

Bulk Drug Output Moves Outside U.S.



Merck worker fills special sterile stainless steel containers with thienamycin antibiotic for shipment to other Merck plants for finishing into dosage forms

Stephen C. Stinson, C&EN New York

World production of bulk drugs for human medicine will hit 530 million lb in 1985, worth $7.9 billion. This volume represents a 4% rise over the 510 million lb produced in 1984. The value is 6% greater than the $7.4 billion of last year. These figures for bulk medicinal chemicals bear no relation to the volumes or manufacturers' values of finished dosage forms or to the eventual retail value of dosage forms. The figures also do not include medicinal chemicals for veterinary, agricultural, or nonmedical uses.

Of the 530 million lb to be produced worldwide this year, only one quarter or 140 million lb will be made in the U.S., although this country will consume one third or 180 million lb of that. This excess of domestic consumption over production continues a long-term trend of decisions, even by American discovery and generic drug firms, to have bulk compounds made outside the U.S.

Western European firms will make 35% or 185 million lb. Countries in Western Europe will consume 32% or 170 million lb. Japanese firms will produce 8% or 45 million lb, and Japan's own pharmaceutical industry will use 4% or 22 million lb. Producers such as those in China and Eastern European countries will make 30% or 160 million lb. All of these countries besides the U.S., Japan, and those of Western Europe will also consume 160 million lb.

Some of the distinctive patterns of drug consumption in different countries have been detailed by Peter Hall of SRI International, Menlo Park, Calif. Hall has studied the bulk medicinal chemical industry as an analyst in SRI's specialty chemical research program. He notes that the Japanese have a relatively high per capita consumption of antibiotics and anticancer drugs. The French lead in consumption of cerebral vasodilator drugs. Use of cardioglycosides for heart disease is high in West Germany.

Hall has characterized the drugs consumed in the largest volumes throughout the world. He notes that 18 bulk medicinals comprise 82% of the volume consumed annually and 40% of the dollar value. These include ascorbic acid (vitamin C, 66 million lb), aspirin (56 million lb), and acetaminophen (31 million lb).

Such bulk drugs tend to be com-

Drug plants need exacting specifications

The changing U.S. climate in drug production and marketing leads to continual building of new plants everywhere in the world. To meet their new plant needs, makers of bulk medicinals and dosage forms call on such companies as Catalytic, Crawford & Russell, and Foster Wheeler, that have special expertise in designing and building pharmaceutical plants. Integrated, multinational drug firms maintain their own engineering and construction divisions. But even these firms contract outside their company when their own divisions are strained to capacity.

One of the largest sellers of engineering and construction services to the drug industry is Foster Wheeler. The Livingston, N.J., company currently has pharmaceutical projects under way worldwide with a total installed cost of almost $800 million. These range from relatively small plants costing several hundred thousand dollars to large plants with price tags of more than $50 million. Foster Wheeler engineers furnish services ranging from site selection and feasibility studies to plant design and materials procurement to plant erection and performance guarantees.

To Tele Gnudi, Foster Wheeler's technical director for pharmaceuticals and fine chemicals, each plant type has its own leading design theme. For production of dosage forms, the theme is product integrity. For organic synthesis of bulk medicinals, the issue is product purity. Sterility is the guiding principle for fermentation plants.

In addition, Gnudi says, Foster Wheeler engineers conceive dosage form plants from the beginning with a view to eventual inspection by the U.S. Food & Drug Administration for adherence to the agency's guidelines for Current Good Manufacturing Practices (CGMP). FDA inspectors resident in other countries also visit plants that will export to the U.S. The agency has not yet applied CGMP to plants that make bulk medicinals. But that future possibility leads Foster Wheeler to design compliance into the product purification sections of such plants. Thus the engineering firm confers with FDA inspectors and outside consultants at the outset of a project.

To ensure product integrity in a tableting plant, for example, Gnudi and his colleagues locate production of different tablets in different rooms. Each room may need its own filtered air supply, which is scrubbed before venting. The Foster Wheeler team specifies room interiors for ease of cleaning, especially the cleaning that accompanies product or machinery changeovers. It studies movements of workers and products, and locates air locks, showers, and locker and uniform rooms with a view to preventing cross-contamination. Some products may need unidirectional personnel paths, in which workers never retrace their steps.

All these measures influence costs of energy management and capital investment. Foster Wheeler engineers study different layouts and schemes of energy management and consult with the client on these implications of the original specification. Another consideration is the "just-in-time" concept of production, in which each component of the packaged dosage form appears at the moment of need to minimize inventories.

In addition to product purity, waste treatment and worker safety are important to synthetic organic bulk medicinal plant design, Gnudi says. Environmental problems are often not so severe as with other fine chemicals plants, because amounts produced are relatively smaller. The plant can sell waste solvents to a scavenger, for example, rather than recover them. But needs for product documentation are greater than for other plant types. Managers must be able to trace a batch in detail.

Sterility is the main issue in fermentation plants, Gnudi points out, because the operator may carry out only 40 fermentations in a fermentor per year. Spoiling one batch by contaminating organisms may result in loss of a product costing $1500 per kg. But worker safety is also important in such plants. Their products can be potent allergens, and exposure may bring severe reactions. Waste treatment is also a factor. Spent broths contain nutrients whose degradation by microorganisms would deplete oxygen in lakes and streams. Sludge must be incinerated or disposed of safely in a landfill.

With all of these details to include in the final design, Gnudi says that Foster Wheeler often gets tantalizingly little information from a potential client about the type of plant desired. Because of drug companies' desires for secrecy, the initial specification may be only that the plant is expected to cost "$10 million to $80 million," contain "30 to 60 reactors of various capacities," and be capable of such special reactions as hydrogenation.

At this stage, Gnudi says, the client contacts many engineering companies to see what experience they have with the plant type, what chemical engineering capabilities they have, and whether they will have the manpower available during the time the plant is to go up. As the list of engineering companies being considered narrows, Foster Wheeler receives increasing information about what the plant is expected to do.

modities with little captive consumption, resulting in a large open market. None of them have much patent protection left. High percentages of them have nonmedicinal uses. For example, although they comprise 82% of bulk medicinals consumed, these compounds amount to only 53% of consumption for medical and dietary use.

Despite their commodity status, the sheer volumes of these bulk drugs lead to high total market values. Two thirds of them have sales of more than $50 million per year. These compounds also tend to have relatively high consumption outside of developed countries.

In contrast to the high-volume bulk medicinals, however, a few well-known drugs have worldwide consumptions measured in hundreds of pounds. Use of the anticancer drug methotrexate is only 360 lb. Consumption of the antihypertensive agent clonidine amounts to 300 lb.

Hall also has identified some of the factors that make for success in producing bulk medicinal chemi-

cals. One factor is captive use for the compounds, which is characteristic of makers of over-the-counter drugs and dosage forms of prescription drugs. On rare occasions after their patents on certain compounds have expired, drug firms will sell bulk compounds to competitors.

A second factor Hall cites is possession of unique chemical processes that competitors are unable or unwilling to undertake. Many drug companies are unwilling to carry out nitrations, for example, because there is constant risk that these reactions will run out of control. Production of organofluorine compounds, reactions at cryogenic temperatures, and fermentative production of steroids and antibiotics are technologies that potential customers may lack.

A third factor for success is sales to countries with little or no patent protection. For example, many developing countries refuse to honor drug patents. And Canadian law compels drug companies to license their patents.

The reasons for the long-term gravitation of bulk drug production away from the U.S. are economic, environmental, and technological. First, production costs in other countries tend to be much lower. Another economic factor is that countries like Italy, Hungary, Poland, and China historically have targeted the bulk drug industry as a source of foreign exchange. Even if some of these overseas producers have since abandoned subsidized pricing and disregard of drug patents as marketing tools, their aggressive entries into the bulk drug market have made them formidable competitors.

A case in point is Italy. At the close of World War II, the government allowed Italian companies to

Volumes of bulk drugs consumed differ by world regions

Millions of lb	U.S.	Western Europe	Japan	Other	Total
Antibiotics	19.4	24.5	4.4	15.1	63.4
Anti-infectives & antiparasitics	6.6	21.1	0.9	42.3	70.9
Cardiovascular agents	1.4	2.3	0.4	2.3	6.4
Central nervous system agents	66.8	40.0	3.3	41.1	151.2
Respiratory agents	3.2	4.0	0.9	2.9	11.0
Steroids	0.1	0.1	a	0.1	0.3
Vitamins	59.0	53.8	9.3	38.1	160.2
Other	2.5	2.9	0.3	1.8	7.5
TOTAL	159.0	148.7	19.5	143.7	470.9

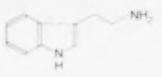
Note: Data for 1982. a About 15,000 lb. Source: SRI International

Indole and Quinoline Derivatives are now available for Pharmaceuticals and Agrochemicals

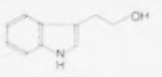
KAWAKEN is the world leader in the manufacture of these chemicals, and want to share our expanding storehouse of knowledge with you. We're ready to take your custom orders.

Indoline

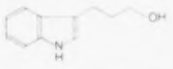
Tryptamine



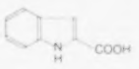
Tryptophol



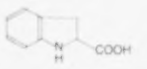
Hornotryptophol



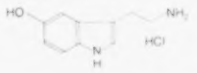
Indole-2-carboxylic acid



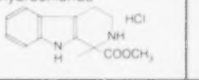
Indoline-2-carboxylic acid



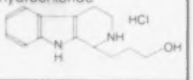
Serotonin hydrochloride



1-Methyl-1-metoxycarbonyl-tetrahydro-ß-carboline hydrochloride



1-Hydroxypropyl-tetrahydro-ß-carboline hydrochloride



1,2,3,4 -Tetrahydroquinoline

5,6,7,8-Tetrahydroquinoline

Decahydroquinoline

1,2,3,4 -Tetrahydroisoquinoline

5,6,7,8-Tetrahydroisoquinoline

Decahydroisoquinoline

For more information write:

KAWAKEN Fine Chemicals Co., Ltd.

6-6, Kobuna-cho, Nihonbashi, Chuo-ku, Tokyo, 103 Japan
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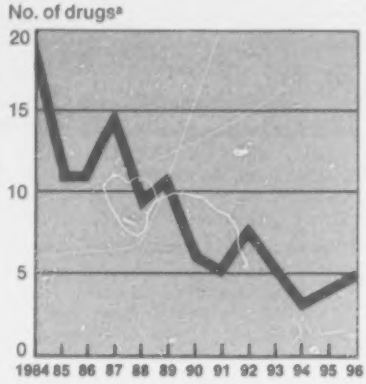
CIRCLE 1 ON READER SERVICE CARD

Number of drugs coming off patent set to decline



[a] Includes allowance for drugs granted 10-year exclusivity under Waxman-Hatch Act.

ignore drug patents in developing their own production. At first, Italian firms simply copied the products and processes of others. These companies graduated to improving chemical processes. Today, the Italian industry has become highly innovative, to which the growing number of anticancer drugs from that country attests. As a member of the European Economic Community, the Italian government has adopted respect for the drug patents of others. But their early technological and new drug discovery capabilities have multiplied the number of Italian bulk drug firms and made them prime candidates to supply the growing U.S. generic drug industry.

Today there are 70 Italian companies that make bulk medicinal chemicals on a consistent basis, says SRI's Hall. Their annual output is worth about $1 billion, 80% of which they export. These Italian firms supply about 50% of the needs of U.S. generic drug companies.

Again, authorities in other countries are often more comfortable with environmental and safety risks of bulk drug production than those in the U.S. Medicinal chemistry can involve nitrations and use of phosgene. Whereas many American firms large and small routinely carry out such reactions safely, it is difficult to gain approval for a new plant.

The early targeting of the bulk drug industry by producers in other countries has given them technological advantages in the making of certain compounds. The making of any one bulk medicinal is a unique problem, itself, so experience carries much weight. Foreign producers also get technological head starts from the expiration of drug patents in other countries sooner than in the U.S. The Canadian compulsory drug patent licensing law also makes it easier for producers there to gain expertise. Even if they cannot yet supply the patent-protected U.S. market for certain compounds, such firms can become the cost-effective producers by the time each patent runs out here.

All of these factors show up in one decision on how to secure a

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CIRCLE 44 ON READER SERVICE CARD

Merck Sharp & Dohme technician prepares blood plasma for hepatitis B vaccine

supply of propranolol for the U.S. generic market. The U.S. patent on propranolol, a best-selling drug (more than $300 million in the U.S. last year) to treat hypertension and heart disease, ran out in 1984. Until then, Ayerst Laboratories division of American Home Products Corp. was alone in marketing its Inderal brand of propranolol here. Lederle Laboratories division of American Cyanamid Co., Chelsea Laboratories, and Martec Pharmaceuticals filed for Food & Drug Administration approval to market generic forms of the drug.

As Martec vice president for operations Udo Vetter explains, there were only three makers of bulk propranolol in the world who had FDA-inspected plants and who had filed Drug Master Files on propranolol with FDA. A Drug Master File includes details of chemical reactions, processes, and raw materials used to make a drug.

The three eligible propranolol producers were the U.K.'s Imperial Chemical Industries (ICI), which had licensed its patent to and supplied Ayerst, Industrie Chimiche Italiane (Ici), and Cosma of Bergamo, Italy. The experience of the Italian firms stemmed from their production for countries in Western Europe, where the patent had expired earlier, and in developing countries, which often ignore drug patents.

Licensing agreements with Ayerst prevented ICI from supplying Martec. Ici had already agreed to supply Lederle, and Martec managers felt that Ici's plant capacity might be unequal to two customers' needs. Cosma offered the additional attraction of a plant dedicated to few products, thus minimizing risks of cross-contamination. To receive FDA qualification to export bulk medicinals to the U.S., Cosma had to have a North American representative, which is ACIC of Toronto, Ont. As North American representative, ACIC holds the Drug Master File for propranolol, follows U.S. regulatory affairs for Cosma, and acts as importer of propranolol.

Vetter explains that as a fledgling marketer of pharmaceuticals in dosage form, Martec could not afford any mistakes with such an important drug. Thus as it became apparent that the Lederle and Chelsea generic products would be approved soon, Martec opened negotiations with a number of well-regarded generic drug houses. The firm reached a marketing agreement with Zenith Laboratories.

Cosma now produces bulk propranolol in Bergamo, and ACIC imports it into the U.S. for delivery to Martec. After Martec chemists do quality control testing on each batch, it is delivered to Schering Corp. Schering does its own testing as it receives each batch, formulates the bulk compound into tablets of 10, 20, 40, and 80 mg, bottles them, and applies the Zenith label to each bot-

THE ROBERT A. WELCH FOUNDATION
CONFERENCES ON CHEMICAL RESEARCH XXIX.
GENETIC CHEMISTRY: THE MOLECULAR BASIS OF HEREDITY
November 4–6, 1985
The Shamrock Hilton Hotel, Houston, Texas

PROGRAM
Paul Berg, Presiding Scientific Advisory Board Member

Monday, November 4, 1985

9:00	**JACK S. JOSEY,** President, Welcoming of Guests.
9:05	Introductory Remarks.
	CONFORMATION ISOMERS OF THE DNA DOUBLE HELIX
9:20	**ALEX RICH**
10:00	**RICHARD DICKERSON**
10:40	Discussion
	TOPOLOGICAL ISOMERS OF THE DNA DOUBLE HELIX
11:05	**JAMES C. WANG**
11:55	Discussion to be led by **NICHOLAS R. COZZARELLI**
	THE PACKAGING OF DNA IN CHROMOSOMES
1:30	**AARON KLUG**
2:30	Discussion to be led by **ABRAHAM WORCEL**
	PROTEIN–RNA INTERACTIONS
3:15	**PETER B. MOORE**
4:05	Discussion to be led by **PAUL SCHIMMEL**

Tuesday, November 5, 1985

	DNA AND CHROMOSOME REPLICATION
9:00	**ARTHUR KORNBERG**
9:50	Discussion to be led by **BRUCE M. ALBERTS**
	RECOMBINATION OF DNA
10:45	**CHARLES M. RADDING**
11:35	Discussion to be led by **HOWARD A. NASH**
12:15	Lunch
1:00	**DUILIO ARIGONI, 1985 WELCH AWARDEE**
	THE TRANSCRIPTIONAL UNIT OF DNA EXPRESSION
2:15	**JAMES E. DARNELL**
3:00	**MICHAEL J. CHAMBERLIN**
	SPLICING OF RNA
3:55	**THOMAS R. CECH**
4:30	**THOMAS MANIATIS**
5:15	Discussion to be led by **PAUL BERG**

Wednesday, November 6, 1985

	CHEMICAL SYNTHESIS OF DNA
9:00	**KEIICHI ITAKURA**
9:40	**MARVIN H. CARUTHERS**
10:40	**MICHAEL SMITH**
11:20	Discussion to be led by **ROBERT LETSINGER**

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CIRCLE 64 ON READER SERVICE CARD

tle. Martec maintains its own employee in Schering's Kenilworth, N.J., plant, who oversees formulation and tableting according to Martec's specified process. Martec's representative recommends each batch of tablets for approval and Schering ships it to Zenith. Acting for Martec, Vetter officially releases each shipment while it is on its way to Zenith. As a large-volume marketer of generic pharmaceuticals, Zenith sells the generic propranolol to such outlets as drugstore chains and other firms that distribute to low-volume users like independent pharmacies. Under its agreement with Zenith, Martec retains the right to sell to hospitals, though Vetter points out that this is not a very important market for propranolol.

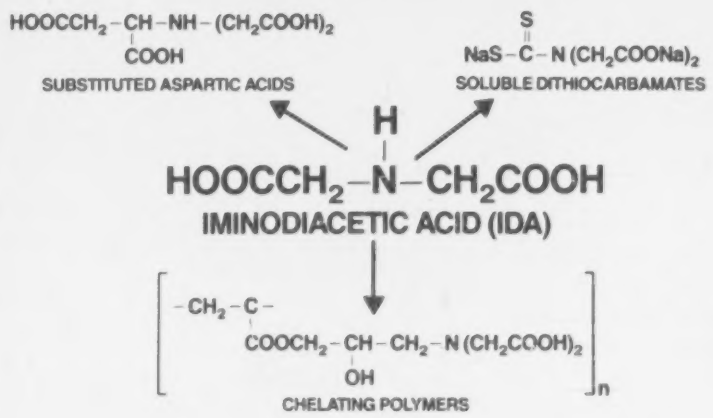
Companies like ACIC are important intermediaries for arranging supplies of bulk drugs for U.S. firms. ACIC represents eight other producers in the burgeoning Italian industry as well as more companies in other countries. But in a turnabout of the historic trend of production moving abroad, ACIC has opened a bulk drug plant in Richmond, Calif., and will start up another in Brantford, Ont., in the beginning of 1986.

The Richmond plant will make chlorpromazine, a major tranquilizer to treat psychosis, and methyldopa, used for hypertension. ACIC's executive vice president Luciano Calenti says, "We feel that the total growth of the market means opportunity in the U.S., if done on the right scale and in the proper way. We can be cost competitive." Calenti adds that a possible fall in the value of the dollar may increase the competitiveness of the California plant.

Calenti says that ACIC has not yet decided on the product slate for the Brantford plant. Products will be chosen according to opportunities under Canada's compulsory drug patent licensing law and in developing countries that do not accept validity of drug patents at all.

Speaking of countries active in selling bulk drugs worldwide, Peter Hall of SRI International says, "Bulk medicinal chemicals supplied by companies in Eastern Europe and

React to this...



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CIRCLE 36 ON READER SERVICE CARD

Eighteen drugs account for 82% of volume consumed

Compound[a]	Value ($ millions)	Consumption (millions of lb) Medicinal	Total
Ascorbic acid	$ 325	36.4	66.1
Penicillin G	240	4.2	18.3
Vitamin E	230	7.2	14.3
Ampicillin	150	3.7	3.7
Aspirin	115	55.6	55.6
Acetaminophen	100	31.3	31.3
Penicillin V	100	1.5	6.8
Riboflavin	90	1.8	4.7
Sulfonamides	90	8.0	11.0
Thiamine	85	3.6	5.5
Niacin & derivatives	65	4.8	19.4
Calcium pantothenate	60	1.8	8.8
Caffeine[b]	45	4.4	9.9
Chlortetracycline	40	0.3	2.5
Pyridoxine	40	2.1	2.6
Tetracycline	35	0.8	2.9
Oxymetracycline	30	1.6	2.6
Theophylline	15	3.0	3.0
TOTAL	$1855	172.1	289.0

a Data for U.S., Western Europe, and Japan only. b Synthetic only.
Source: SRI International

China for world markets are small compared with other regions, but production is growing rapidly and is particularly significant in terms of price competition with Western Europe and the U.S."

In the U.S., China is represented by Sinochem in New York City. Hall calls China an important supplier of acetaminophen analgesic, broad-spectrum antibiotic chloramphenicol, and diosgenin, which is a plant-derived steroid that can be converted to such steroid drugs as betamethasone and dexamethasone.

Medimpex North America, New York City, represents firms in the Hungarian pharmaceutical industry, which has a long history. Perhaps the oldest is Chemical Works of Gedeon Richter, which started in 1901 by extracting drugs from plants. Richter products include cardiac glycosides, steroids, ergot alkaloids, anticancer drugs related to vinblastine, and synthetic organic chemical drugs. Chinoin Pharmaceutical & Chemical Works began by extracting codeine and morphine alkaloids from poppy straw and seed and making B vitamins by fermentation. Most of Chinoin's current products are synthetic organics, and most of the Hungarian alkaloid business is handled by Alkaloida Chem-

Double-barreled law may boost bulk drug sales worldwide

A new law passed by Congress late last year indirectly may increase the number of bulk medicinal chemicals produced, raise worldwide levels of production, and shift production sites geographically. These effects could result because competition from generics has forced discovery companies to redouble their research efforts to find new, patent-protected compounds. To sustain their growth, generics houses have had to begin their own pioneering research to survive an expected crunch in the 1990s. Their research also will increase the number of new compounds. Intensified work on new, patent-protected dosage forms and drug delivery systems may prolong life cycles of old compounds, sustaining their production in bulk. Lower prices for generics could increase worldwide demand, leading to higher production of bulk compounds. These changes in demand for bulk medicinals could either accelerate the shift of production away from the U.S. to Europe and the Far East, or they could tempt U.S. firms to reassert this country's leadership in drug manufacture.

The Drug Price Competition & Patent Term Restoration Act of 1984 was the brainchild of Rep. Henry A. Waxman (D.-Calif.) and Sen. Orrin G. Hatch (R.-Utah). It both eases Food & Drug Administration approval of generic forms of off-patent drugs and extends patent lives of drugs by amounts of excessive time spent in gaining FDA approval. Congress passed the law a year ago, and it became effective last November.

To gain FDA approval, the generic marketer now files an Abbreviated New Drug Application (ANDA). The medical use, ingredients, strength, labeling information, and dosage form must be the same as those approved for the original, brandname drug. The generic marketer also must file results of tests showing that the generic form is bioequivalent to the original drug. A Drug Master File (DMF), which includes details of synthesis, raw materials, and names of producers of intermediates and bulk drug, also must be submitted. Generic marketers may now use the drug to do bioequivalency tests and develop the DMF before the patent expires without being accused of violating the patent.

There are some exceptions to ease the transition for brandname drug firms. For example, an ANDA may not be granted for 10 years for new chemical entities approved for the brandname firm between Jan. 1, 1982, and Sept. 24, 1984. Thus the patent on Pfizer's Feldene brand of piroxicam anti-inflammatory expires in 1988, but no ANDA will be granted before 1992, because FDA approved Pfizer's New Drug Application (NDA) in 1982. Also, no ANDA may be granted for two years for drugs or formulations whose supplemental NDAs were approved between Jan. 1, 1982,

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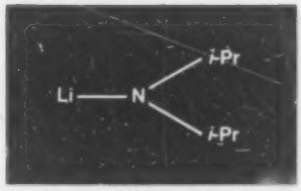

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CIRCLE 73 ON READER SERVICE CARD

ical Factory. Other Hungarian bulk drug firms are Biogal Pharmaceutical Works and Egis Pharmaceuticals.

Any firm hoping to export bulk drugs to the U.S. must have its plant inspected by FDA for adherence to the agency's Current Good Manufacturing Practices. FDA does not maintain resident inspectors outside the U.S. Rather inspectors knowledgeable in plants of a certain type make 30-day tours to particular regions of the world to see plants of that type. Tours have included Eastern Europe and China. In addition, FDA recognizes plant approvals by Canadian, Swedish, and Swiss inspectors in those countries.

Perhaps the biggest factor affecting U.S. production and marketing of bulk medicinal chemicals has been the passage of the Drug Price Competition & Patent Term Restoration Act of 1984. This law has the potential to increase world levels of bulk drug production, reverse the flow of bulk drug production away from the U.S., or to accelerate that flow. The law took effect only in November 1984, so it is too soon to judge the net effects it will have.

One section of the law makes it easier for firms to gain FDA ap-

and Sept. 24, 1984. Thus all present tablet strengths of generic propranolol for heart disease and hypertension may be approved now except 60 mg, which must wait until mid-1986.

To gain an extension of a patent, the patent holder applies to the Patent & Trademark Office. The patent office asks FDA to verify the amount of time the drug spent in regulatory review and publishes the proposed extension in the *Federal Register*. Challengers have 180 days to argue that the applicant itself caused delays by failing to be diligent. To be eligible, the patent must still be in force; may cover a compound, use, or production process; and can be extended only once. The extension is limited to half the time the drug spent as an Investigational New Drug at FDA. It cannot exceed five years. And the sum of the patent life after NDA approval and the extension cannot exceed 14 years.

There have been delays in implementing Waxman-Hatch owing to the flood of paperwork, lack of sufficient staff in the offices involved, and defects in filings. About 600 ANDAs have been filed by generic marketers in the past 10 months. The first approval came on Feb. 1, 1985, for Biocraft Laboratories to market disopyramide for abnormal heart rhythms. FDA officials say that the Division of Generic Drugs is now fully staffed, and that the backlog began to break loose in midsummer. There have been a total of seven major generic drugs approved this year. The latest is diazepam, the generic form of the popular tranquilizer Valium (C&EN, Sept. 9, page 5).

The patent office has received 28 applications for patent extension, of which it denied 16. Ironically, the first approval was for a nuclear magnetic resonance scanner, whose wait for patent extension may be granted in October. The first company whose drug patent may be extended is Pharmacia of Sweden, which may get 473 more days' protection for its Promit brand of injectable dextran solution on Sept. 29.

proval for generic dosage forms of drugs whose patents have expired here. The other section lets discovery companies apply for extensions of the lives of their U.S. drug patents in proportion to the amount of time those drugs spent in FDA approval procedures.

One effect of the law may be to stimulate U.S. discovery companies to redouble their research efforts to develop new compounds, which can then get patent protection. Even before passage of the law easing generic approval, domestic discovery drug firms increased their research spending 17% per year to $3.25 billion in 1984 from $1.75 billion in 1980. These increases were in response to the double crunch of large numbers of compounds discovered in the 1960s coming off patent in the 1980s, combined with the relatively sparse discoveries of the 1970s.

And U.S. pioneer drug firms can take little comfort in the part of the law that extends patent lives for many of their compounds. To date, extensions applied for are measured in hundreds of days rather than in years. The easier Abbreviated New Drug Application procedures set up by the law far outweigh benefits of such marginal extensions. Thus the impetus to increase pioneering research remains. To the extent that these research efforts are successful, commercialization of the new compounds will raise total bulk drug production worldwide.

Ironically, another effect of the law has been to force generic drug firms to begin pioneering research to develop new compounds. This is because generic houses can expect the backlash of the paucity of new compounds that came out of the discovery companies in the 1970s. The number of drugs coming off patent in the U.S. peaked at 19 in 1984 and will decline to five in 1996. These are the compounds from which new generic dosage forms can be selected. To sustain their growth, generics firms must take up the slack by discovering their own compounds.

The effort is under way. Mylan Laboratories of Pittsburgh, a well-known marketer of generic drugs,

Continued on page 50

SYNTHESIS

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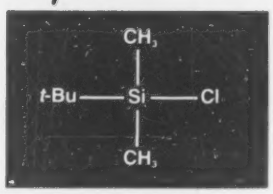

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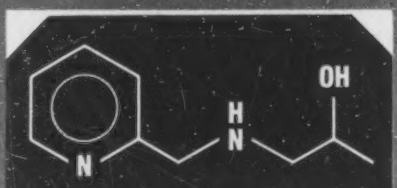

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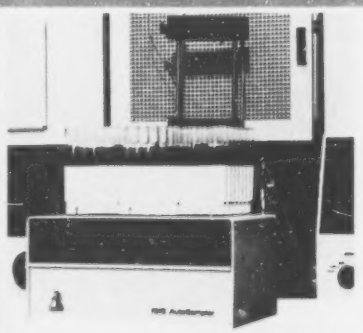

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Product Report

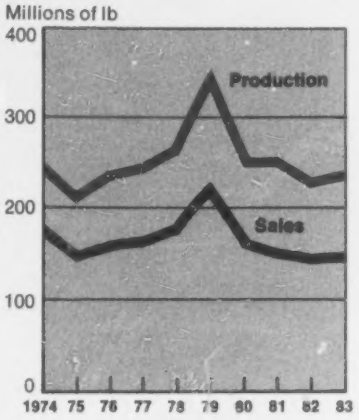
recently got FDA approval of a New Drug Application to market a drug for hypertension that contains 60% triamterene and 40% hydrochlorothiazide. The company says that this proportion is more effective and the dosage form more available for absorption than the competing brand-name 2:1 product of SmithKline Beckman. Mylan president Milan Puskar says the company also has new compounds in research.

Rugby Laboratories of Rockville Center, N.Y., which is perhaps the biggest U.S. marketer of generics, also has a number of new compounds in the pipeline, says chairman Michael Ashkin. And Udo Vetter of Martec says that his firm, recently founded to market generics, has begun pioneering research. This turn to pioneering research by generics firms will raise the level of such research here, increase the chances of finding new compounds, and lead to bulk production of any such finds.

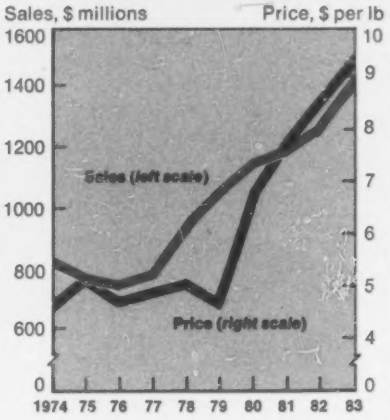
Another effect of the law may be to heighten searches by pharmaceutical companies for new, patentable dosage forms for their older compounds. Among developments in this area, drug firms are steadily signing up to formulate their compounds around the controlled-release technology of Pennwalt Corp.'s Pharmaceutical Division. This technology binds drugs to cationic or anionic ion exchange resin beads, which are then encased in ethylcellulose membranes.

Again, the recently founded Elan of Ireland is a company whose business is to develop alternative, improved formulations for its clients. The company gains approval from Irish authorities to test new formulations of already approved compounds in healthy volunteers more quickly than American firms can from FDA. Insofar as its services to the American drug industry are concerned, Elan verifies performance of the optimum formulation for a particular compound's chemistry and therapeutic use, and turns the information over to its clients for them to take through FDA. A U.S. subsidiary, Elan Pharmaceutical Research of Gainesville, Ga., has the capacity to produce the dosage form if desired.

U.S. medicinal chemicals volume has leveled off . . .



. . . but rising prices have caused value to increase



Source: International Trade Commission

For doctors, the attraction of controlled drug release is once-a-day doses for chronic illnesses. Having to take their medicine only once daily may increase the likelihood that patients will keep up their medication in comparison with more complex schedules. To the extent that reformulation of older compounds is successful, the life cycle of older compounds will be longer, sustaining their worldwide production in bulk.

Though effects of the law seem to be to raise future levels of bulk drug production volumes, the effects on value are mixed. New, patent-protected compounds from pioneering research can command relatively higher prices in bulk, thus contributing to a rise in overall value. Conversion of older compounds to generics will lead to searches for lower-priced bulk compounds, which will tend to lower overall value.

Although there are many factors that could raise worldwide bulk drug production volume, there is a question of where it is to occur. Here again, one effect of the new law on easier generic drug approval is an opportunity to shift production back to the U.S. This is because there will be a momentary shortage of the worldwide, multipurpose, FDA-approved plant capacity needed, as domestic marketers of generics look about for supplies of the 56 compounds that will come off patent in the U.S., from 1984 (when the law became effective) through 1987.

Propranolol is a case in point. Martec was left with only one choice among three world suppliers when production of the other two was spoken for. To develop a domestic source, the relative newcomer Martec would have to convince an American company that it was a responsible bearer of costs of equipment, process development, and creation of the Drug Master File. Prices for bulk propranolol would be at least twice those of Cosma's.

A future development that also could cause the U.S. generic drug industry to look to domestic sources is a proposed bill forbidding imports of products made by processes that are patented in the U.S. This bill is sponsored by Sen. Charles Mathias (R.-Md.) and Sen. Frank Lautenberg (D.-N.J.). Bulk drug makers continually perfect their chemical processes; thus, patents on processes could expire here later than those on compounds themselves.

The proposed process patent law would make buyers of imported products liable for infringements of U.S. process patents by overseas suppliers. Unable to be sure in advance if a foreign bulk drug maker was using a process patented in the U.S., American generics firms might be wary of litigation and not import the drug.

The bill's strongest supporters are Allied Corp. and Corning Glass

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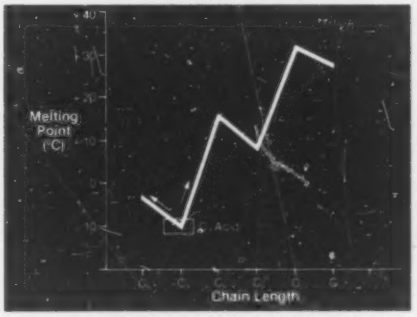

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Medicinal chemicals: definitions

The medicinal chemicals covered in this report are those for human medicine alone. They are made by organic synthesis, isolation from plant and animal sources, and extraction from fermentation broths. They exclude amounts for veterinary, agricultural, or nonmedical use. Not covered, for example, are vitamins, steroids, or antibiotics for animal feeds, or quinine for tonic water. Also excluded are substances not easily expressed in pounds of chemical entities such as vaccines and blood clotting factors.

Among human medicinal chemicals are antibiotics to treat bacterial infections. These include aminoglycosides such as gentamycin, cephalosporins such as cephalothin, the natural penicillin G and the semisynthetic ampicillin, and tetracyclines. Such sulfa drugs as sulfadiazine are used to prevent bacterial infections. Chloroquine is an antiparasitic against malaria.

Cardiovascular agents treat high blood pressure and heart disease. Among antihypertensives are Rauwolfia alkaloids like reserpine. Hydrochlorothiazide is a diuretic, which lowers blood pressure by increasing urine production. Such cardiac glycosides as digoxin stimulate heart beat. Propranolol is a β-blocker used to treat both abnormal heart rhythms and hypertension.

Agents active in the central nervous system include the analgesic aspirin, the nonsteroid anti-inflammatory agent ibuprofen, the minor tranquilizer diazepam, the major (antipsychotic) tranquilizer thioridazine, the antidepressant imipramine, the sedative phenobarbital, the antiepileptic valproic acid, and L-dopa, used to treat Parkinson's disease.

Drugs classed as respiratory agents include the antihistamine chlorpheniramine for "stuffiness" and theophylline for asthma. Among steroids, corticosteroids are also used for asthma and to treat inflammatory diseases like arthritis. As steroid sex hormones, progestogens and estrogens go into birth control pills.

Medicinal chemicals also include vitamins. Methotrexate is an important anticancer drug. Oral tolbutamide maintains good blood sugar levels in many adult-onset diabetics, who thus avoid the need for insulin injections. Cimetidine has revolutionized treatment of ulcer patients.

Works. Allied is discontented with current laws to inhibit imports of its patented amorphous metal alloys. Corning has been fighting imports of fiber optics materials whose process of manufacture infringes its patents.

Leading the fight against the process patent bill for U.S. generic drug marketers is the Generic Pharmaceutical Industry Association. According to GPIA president Dee Fensterer, present remedies to sue over domestic patent infringement and to petition the International Trade Commission to exclude infringing imports are adequate. Moreover, the proposed bill would no longer require patent holders to use their U.S. patents in this country to gain protection. It would also enable a U.S. producer to shut out imports made by a certain process overseas by patenting that process for the first time here. And the bill could subject importers to legal costs even if they won suits over process patent infringement.

The U.S. bulk medicinal chemical production industry numbered 92 firms in 1983, according to the International Trade Commission, which has not published figures later than that year. This number is not much changed from the 99 companies ITC listed in 1973. Of the 540 chemical entities ITC counts as medicinal chemicals, 428 were made by only one producer, 82 had two producers, 24 had three producers, four had four producers, and only two compounds, phenylpropanolamine and feed-grade choline chloride, had as many as five producers.

But if the number of U.S. producers has declined slightly through the years, volume has fallen off more sharply. Production of bulk medicinal chemicals peaked at 313 million lb in 1979, according to ITC, and had leveled off 25% lower at 233 million lb by 1983. These figures

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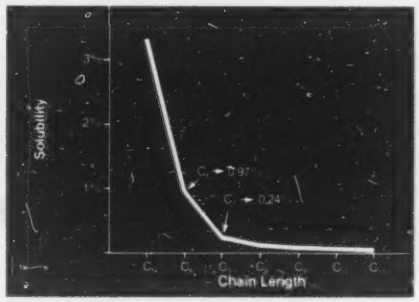

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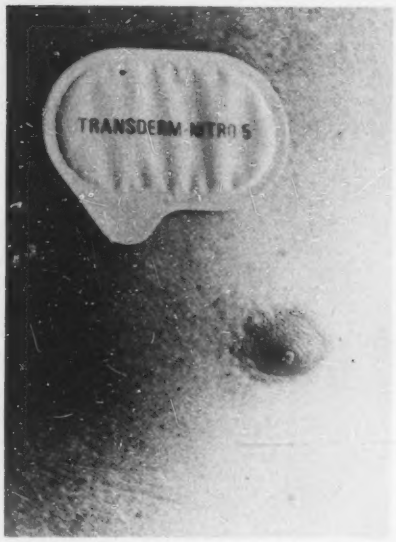

Ciba's nitroglycerin patch is example of one of industry's new dosage forms

include production for applications other than strictly human medical use.

A shift toward domestic production could come from generic pharmaceutical companies themselves. Biocraft Laboratories is a well-known generic house that has long produced penicillin-type antibiotics at Waldwick, N.J., by fermentation and semisynthetic modification. Asked whether his company might integrate back into chemical production of bulk compounds, Puskar of Mylan says, "That's run through our minds." But Rugby's Ashkin is less optimistic about being able to get local approvals for location of a synthetic organic chemical plant in populous areas, and cites difficulties in getting a qualified workforce in less populous ones.

For the distant future, biotechnology could exert significant influences on bulk medicinal chemical production worldwide. As SRI's Hall puts it, biotechnology could lead to changes in the way that bulk drugs are made. Hall also points out, however, that research in this area could lead to therapies other than those now achieved by synthetic organic compounds.

As examples of things to come for old compounds by new methods, Hall notes that Eli Lilly already produces human insulin from cultures of *Escherichia coli* that have been genetically modified to make it. And Bristol-Myers is developing genetically engineered streptomycetes to make the antibiotic amikacin directly as a replacement for current production of amikacin by chemical conversion of kanamycin. He also points to mammalian cell cultures as sources of interferon, antiviral vaccines, and urokinase, an enzyme used to dissolve blood clots in blood vessels of the lungs. And Hall says that plant cell cultures might become sources of compounds now obtained by harvesting and extraction of plants themselves. For example, Mitsui Chemical Industries makes alkannin, a naphthoquinone antibacterial and anti-inflammatory compound, from plant cell cultures.

Another observer who has studied the potential of biotechnology in medicinal chemicals is Philip Rotheim of Business Communications Co., Stamford, Conn. Rotheim divides biotechnology into "old" and "new." Under old biotechnology, he puts fermentations with wild or mutated microorganisms; conversion of precursors to such products as steroids, vitamins, semisynthetic antibiotics, and 6-aminopenicillanic acid; and extraction of products from plant, animal, and human sources. For Rotheim, new biotechnology involves recombinant deoxyribonucleic acid, cell fusion, and plant and animal cell cultures. He links the two biotechnology types, saying that the recent blossoming of the new has led to a renewed interest in developing the possibilities of the old.

Rotheim estimates that bulk pharmaceutical products from old biotechnology will grow at 0.6% annually to $7.46 billion in 1989 from $7.28 billion in 1984. From a smaller base, he forecasts a 27.5%-per-year increase to $186 million in 1989 from $55.3 million in 1984 for bulk pharmaceutical products from the new. Most of this growth will be in insulin from recombinant DNA. Other products Rotheim expects from the new biotechnology by 1989 include human growth hormone, tissue plasminogen activator, and interferon. In the 1990s, he predicts appearance of blood anticlotting factors and hormone-releasing hormones, and therapeutic monoclonal antibodies. □

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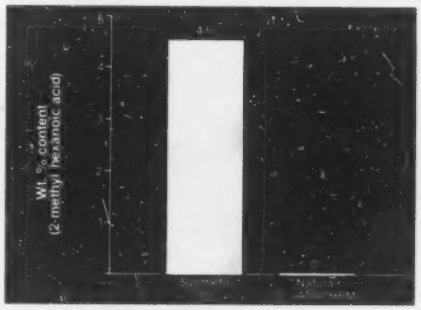

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